Usefulness of NT-proBNP in assessment of right ventricular function in children after tetralogy of Fallot correction – a preliminary study

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Abstract

Background: Although surgical treatment for tetralogy of Fallot (TOF) has been used with considerable success, right ventricular function may remain altered after repair. The NT-proBNP assessment has been shown to be a reliable parameter for the heart failure assessment.

Aim: To determine NT-proBNP values in assessment of right ventricular function in children after TOF correction.

Methods: In 20 patients after TOF correction aged from 10 to 17 years (follow-up period ranged from 7 to 16 years) NT-proBNP level at rest and after exertion, treadmill test and echocardiography were performed. In the control healthy children NT-proBNP level at rest was assessed.

Results: The mean values of NT-proBNP level in the TOF patients were significantly higher than in controls (11.0 ± 12.0 fmol/l and 5.4 ± 7.5 fmol/l, $p < 0.05$). In patients repaired with a transannular patch the mean value of NT-proBNP level was higher than in children operated on without a transannular patch (18.3 ± 16.5 vs. 6.8 ± 7.9 fmol/l, $p < 0.05$). In children in whom physiological shortening of QRS complex during treadmill test was observed, NT-proBNP level was lower (mean values at rest 5.0 ± 4.8 fmol/l and after exertion 7.3 ± 6.3 fmol/l) compared to patients with prolongation of QRS duration (mean values at rest 17.7 ± 15.6 fmol/l and after exertion 20.3 ± 17.8 fmol/l) ($p < 0.05$). Significant differences in NT-proBNP levels between children with severe pulmonary regurgitation and mild/moderate pulmonary regurgitation were detected (mean values at rest 18.6 ± 15.0 vs. 4.2 ± 3.9 fmol/l and after exertion 20.0 ± 18.6 vs. 5.7 ± 4.6 fmol/l) ($p < 0.05$). The NT-proBNP levels were also higher in children with severe tricuspid valve insufficiency compared to children with mild/moderate tricuspid valve regurgitation (mean values at rest 19.5 ± 15.0 vs. 4.9 ± 3.7 fmol/l and after exertion 22.5 ± 17.1 vs. 7.0 ± 4.6 fmol/l).

Conclusions: The NT-proBNP level in patients after TOF correction is higher than in healthy children. The NT-proBNP level is higher and exertion tolerance is lower in children repaired with rather than without transannular patch. In patients with severe pulmonary regurgitation and/or severe tricuspid valve insufficiency NT-proBNP level is higher than in patients without right ventricular volume overload. The measurement of NT-proBNP level might be helpful in order to separate those patients after TOF correction who are at increased risk of heart failure and arrhythmia.

Key words: tetralogy of Fallot, NT-proBNP, transannular patch

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Introduction

Surgical outcomes in tetralogy of Fallot (TOF) treatment are very satisfactory; over 94% of patients survive 25 years after the operation [1]. In spite of great progress in therapeutic strategies of TOF, residual interventricular septal defects, advanced pulmonary and tricuspid insufficiency, secondary right ventricular (RV) outflow tract obstruction and potentially fatal arrhythmias after total surgical correction are relatively frequently encountered [1, 2].

Currently, the most significant complication is pulmonary valve regurgitation which, according to long-standing observations, engenders impairment of cardiac haemodynamic function. The increased risk of severe pulmonary insufficiency occurs especially in the case of operative technique using transannular patch. Timely pulmonary valve replacement improves not only haemodynamic conditions but also electrical conduction, which is disturbed in patients with ventricular overload [3-5]. The universally accepted system to describe

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the progression of heart failure is the NYHA scale based on symptoms reported by patients, which do not always correlate with the actual severity of haemodynamic dysfunction. Furthermore, conventional Doppler echocardiography in assessment of RV function, in view of its complicated geometry, turns out to be inaccurate, while magnetic resonance imaging (MRI), considered the gold standard in diagnostics, is not currently universally accessible, which makes it impossible to include in daily clinical practice.

Recently, many authors reported on the additive diagnostic and prognostic value of N-terminal pro brain natriuretic peptide (NT-pro BNP) in assessing the risk of heart failure progression in patients with impaired RV function [1, 6-8]. The purpose of our study was to evaluate the role of long-term NT-proBNP evaluation in the assessment of RV function in children after total TOF correction.

Methods

Investigated group

The study included 20 patients aged 10-17 years who were hospitalised from January to June 2008 and were 7-16 years after total TOF correction. The control group consisted of 20 healthy children age and gender-matched with TOF patients. The main characteristics of the study and control groups are presented in Table I. The TOF group was divided into two subgroups according to the operative technique used: 8 children had transannular patching performed whereas the remaining 12 children did not.

Follow-up strategy

In all patients a unified scheme of investigation was used that contained detailed history taking, physical examination with special focus on cardiovascular capacity evaluation based on the NYHA scale, and information on operative technique, history of consciousness disturbances and basic parameters such as heart rate and blood pressure.

NT-proBNP level measurement

In the TOF group NT-proBNP plasma level was measured at rest and on exertion during the treadmil test, while in the control group the measurement was performed at rest only. For the measurement the enzyme immunoassay method (ELISA) was adopted and the results were expressed in femtomol/litre (fmol/l). All measurements were performed immediately after taking blood and its centrifugation (during 1 hour).

Treadmill test

Treadmill test was carried out according to Bruce protocol and was terminated on patients' request due to fatigue precluding exercise continuation. During the test continuous 12-lead ECG monitoring was performed. Heart rate and blood pressure were measured before and after the exercise test and also at the end of each protocol phase. Blood pressure was measured using the oscillatory method on the patient's right arm and with a manometer integrated with the treadmill test unit. Among analysed parameters were also exertion duration and the width of the QRS complex in limb lead II both before and after the test.

Echocardiography

Echocardiography with conventional and colour Doppler flow visualisation was performed simultaneously with limb lead II ECG. The procedure was performed by the same investigator in all patients. The following parameters were assessed: RV diameter in M-mode visualisation, degree of tricuspid and pulmonary valve insufficiency progression, and pressure gradient between RV and pulmonary artery using Doppler imaging. For tricuspid and pulmonary insufficiency assessment the semi-quantitative method was elected, quadruple- and triple-degree respectively. In patients with maximal pressure gradient between RV and pulmonary artery > 25 mmHg RV outflow tract obstruction (RVOTO) was recognised.

Statistical analysis

Mean values and standard deviations were calculated for all quantitative variables. Differences between average values were assessed using the Mann-Whitney test. All assumptions were verified with statistical significance set at $p < 0.05$. All assays were analysed bilaterally.

Results

Eight of 20 children from the TOF group complained of mild limitation of exercise tolerance. In one child episodes of syncope were observed. On the basis of detailed analysis of data from patients' history, they were all enrolled in group I according to the NYHA classification. Basic life parameters (heart rate, blood pressure) were within normal limits in all patients except one boy in whom increased blood pressure values were found, although 24-hour ambulatory BP monitoring (ABPM) did not confirm these observations.

Average plasma NT-proBNP level at rest was 11.0 ± 12.0 fmol/l in the TOF group and 5.4 ± 7.5 fmol/l in

Table I. Main characteristics of the study groups

	TOF group (average ± SD)	Control group (average ± SD)
Age [years]	13.5 ± 2.7	13.8 ± 2.4
Boys/girls [number of patients]	12/8	12/8
Age at the time of TOF correction [months]	21 ± 13	–
Duration of follow-up [years]	11.5 ± 2.5	–
Body weight [kg]	44.6 ± 13.5	44.8 ± 14.5

the control group. The difference was statistically significant ($p < 0.005$). A significantly higher NT-proBNP levels, both at rest and on exertion, were found in the subgroup after TOF correction using a transannular patch than in patients who underwent TOF correction without a patch (Table II).

Comparison of the results of exercise testing in the TOF subgroups are shown in Table III. The patients after correction with the transannular patch presented lower exercise tolerance than children without the transannular patch.

In 10 patients from the TOF group physiological shortening of QRS complex duration was observed on exertion and the NT-proBNP levels in these children were at rest 5.0 ± 4.8 fmol/l and 7.3 ± 6.3 fmol/l after exertion. In the remaining 10 TOF patients abnormal QRS prolongation was recorded on exertion. In those children NT-proBNP level at rest and after exercise was 17.7 ± 15.6 fmol/l and 20.3 ± 17.8 fmol/l respectively. The differences in NT-proBNP levels between patients with and without QRS prolongation were significant both at rest and after exercise ($p < 0.05$).

The correlation between NT-proBNP levels and selected echocardiographic parameters is presented in Table IV. Third degree pulmonary valve regurgitation was associated with higher NT-proBNP levels, both at rest and after exercise ($p < 0.005$).

Fourth degree tricuspid valve insufficiency was not observed in the study group. However, in patients with third degree regurgitation both at rest and after exercise NT-proBNP levels were higher than in children with first and second degree of tricuspid insufficiency. This difference was significant ($p < 0.005$) (Table IV).

In 17 patients from the TOF group in whom RV enlargement was present in echocardiography, NT-proBNP levels at rest and after exertion were higher than in 3 patients with normal RV (12.3 ± 13.4 fmol/l and 14.7 ± 15.3 fmol/l versus 2.3-7.0 fmol/l and 4.2-9.0 fmol/l, respectively).

Pulmonary valve stenosis was detected in 4 patients in whom NT-proBNP levels oscillated between 2.5 fmol/l and 21.3 fmol/l at rest and between 3.5 fmol/l and 26.3 fmol/l after exercise.

In 16 children with a pressure gradient below 25 mmHg between the RV and pulmonary artery mean NT-proBNP levels at rest and after exercise were 11.0 ± 14.2 fmol/l and 13.5 ± 15.6 fmol/l, respectively.

Discussion

The NT-proBNP is associated with ventricular and atrial distension (including RV). Our data indicated a significantly higher NT-proBNP level in patients after TOF total correction than in the healthy population. According to some publications, the increase of NT-proBNP level is independent of clinical manifestation [6, 9]. Norozi et al. [10], showed that NT-proBNP is one of three (along with Tei-index in echocardiography and maximum oxygen uptake in exercise test) markers of early RV dysfunction, even before clinical symptoms occur.

As our data indicated, the operative technique used in TOF correction affects not only exercise tolerance but also NT-proBNP secretion. Mean levels of this marker were higher in patients operated on with transannular patch application than in children in whom the patch was not used. No data in literature on the correlation between NT-proBNP level and operative technique used in TOF correction has been published.

In a study by Ishii et al. [6] the rise of NT-proBNP level after exertion was particularly high in patients with severe pulmonary and tricuspid insufficiency. According to the literature, RV volume overload is universally accepted among the strongest risk factor of heart failure in patients

Table II. Comparison of NT-proBNP levels in patients after TOF correction with and without transannular patch application

	Operative technique	Mean value ± SD	p
NT-proBNP at rest [fmol/l]	correction without transannular patch application	6.8 ± 7.9	0.05
	correction with transannular patch application	18.3 ± 16.5	
NT-proBNP after exertion [fmol/l]	correction without transannular patch application	8.6 ± 8.0	0.05
	correction with transannular patch application	21.9 ± 19.1	

Table III. Results of exercise test in investigated group

Patients (n = 20)	HR at rest [beats/min]	Max HR [beats/min]	Duration [min]	Metabolic equivalent [MET]	HR limit [%]
Patients after correction without transannular patch application	84 ± 17	167 ± 17	10.25 ± 1.8	10.9 ± 1.4	80.8 ± 8.1
Patients after correction with transannular patch application	89 ± 10	150 ± 23	7.8 ± 1.1	8.9 ± 1.6	70.6 ± 10.5
p	> 0.05	> 0.05	< 0.05	< 0.05	> 0.05

Table IV. Correlation between NT-proBNP level and echocardiographic parameters in TOF group

	General population	Pulmonary valve insufficiency		Tricuspid valve insufficiency	
		I/II°	III°	I/II°	III°
Number of patients	20	11	9	12	8
NT-proBNP at rest [fmol/l]	11.0 ± 12.7	4.2 ± 3.9	18.6 ± 15.0*	4.9 ± 3.7	19.5 ± 15.0*
NT-proBNP after exertion [fmol/l]	13.4 ± 14.2	5.7 ± 4.6	20.0 ± 16.8*	7.0 ± 4.6	22.5 ± 17.1*

** p < 0.005 – grade I/II regurgitation versus grade III regurgitation*

after total correction of TOF [2, 4, 5]. In a study by Festa et al. [11], NT-proBNP level was increased in patients with RV pressure overload. According to our data, in patients with third degree pulmonary valve insufficiency NT-proBNP level both at rest and after exercise was markedly higher than in children with first or second degree regurgitation. Statistical analysis could not be adopted to assess the relationship between NT-proBNP level and RV diameter or maximal pressure gradient, because of the small number of patients with pulmonary stenosis and proper RV diameter.

The QRS complex prolongation (right bundle branch block, RBBB), prolonged QT interval, increased QT dispersion, and the lack of physiological shortening of QRS complex and QT interval duration on exertion are the most frequent ECG findings encountered in patients after TOF correction [12-16]. Budts et al. [17] reported that decreased exercise tolerance in individuals with abnormal prolongation of QRS complex on exertion was associated with subclinical heart failure. Furthermore, abnormal QRS changes during exercise test are a marker of electrical instability of the cardiac muscle and the risk of sudden cardiac death, mainly due to ventricular arrhythmias [18, 19]. Until now, no studies concerning NT-proBNP level and QRS duration at rest and after exercise have been published. The increased NT-proBNP level in patients with abnormal QRS prolongation on exertion, which was demonstrated in our study, indicates that this neurohormone may be an early marker of heart overload and can have additive prognostic value in sudden death risk evaluation. Therefore, further studies are needed to confirm the association between NT-proBNP level and prevalence of arrhythmia in patients after TOF correction.

Study limitations

Assessment of RV diameter in M-mode ECHO visualisation, in view of the complicated geometry of this cardiac chamber, is of limited accuracy. To enhance reproducibility all echo examinations were conducted by the same person. The small size of the investigated population enrolled in the study is also a limitation.

Conclusions

The NT-proBNP level in patients after TOF correction is higher than in healthy children. The NT-proBNP level is higher and exertion tolerance is lower in children repaired with rather than without transannular patch. In patients with severe pulmonary regurgitation and/or severe tricuspid valve insufficiency NT-proBNP level is higher than in patients without right ventricular volume overload. The measurement of NT-proBNP level might be helpful in order to separate those patients after TOF correction who are at increased risk of heart failure and arrhythmia.

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Ocena przydatności NT-proBNP do oceny funkcji prawej komory serca u dzieci po korekcji chirurgicznej tetralogii Fallota – doniesienie wstępne

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Streszczenie

Wstęp: W ostatnim czasie pojawiają się doniesienia o dużej przydatności N-końcowego produktu rozpadu prekursora mózgowego peptydu natriuretycznego (NT-proBNP) w ocenie i prognozowaniu ryzyka wystąpienia niewydolności serca u chorych z zaburzeniami funkcji prawej komory serca, u których stwierdza się podwyższone stężenie tego neurohormonu w surowicy w spoczynku, a także nadmierny jego wzrost w czasie wysiłku w porównaniu z populacją ogólną.

Cel: Ocena przydatności N-końcowego produktu rozpadu prekursora mózgowego peptydu natriuretycznego (NT-proBNP) do oceny funkcji prawej komory serca u dzieci w okresie odległym po korekcji tetralogii Fallota (ang. *tetralogy of Fallot*, TOF).

Metody: Badaniem objęto 20 chorych w wieku od 10–17 lat. Czas obserwacji po korekcji wyniósł 7–16 lat. Grupę kontrolną stanowiło 20 zdrowych dzieci w wieku 10–17 lat. Wykonano następujące badania: ocena spoczynkowego stężenia NT-proBNP w grupie badanej i kontrolnej, test wysiłkowy z pomiarem stężenia NT-proBNP bezpośrednio po wysiłku oraz badanie echokardiograficzne w grupie badanej.

Wyniki: Średnie stężenie NT-proBNP w spoczynku w grupie badanej wyniosło 11,0 ± 12,0 fmol/l, natomiast w grupie kontrolnej 5,4 ± 7,5 fmol/l ($p < 0,05$). Stwierdzono wyższe wartości stężenia NT-proBNP u chorych operowanych z użyciem łaty przezpierścieniowej w porównaniu z chorymi operowanymi bez jej użycia (odpowiednio: 18,3 ± 16,5 i 6,8 ± 7,9 fmol/l, $p < 0,05$). U 10 dzieci z grupy badanej obserwowano fizjologiczne skracanie czasu trwania zespołu QRS w czasie wysiłku. Stężenie NT-proBNP wyniosło u nich w spoczynku średnio 5,0 ± 4,8 fmol/l, a po wysiłku 7,3 ± 6,3 fmol/l. U 10 pozostałych chorych w grupie badanej zaobserwowano nieprawidłową reakcję QRS na wysiłek w postaci wydłużania czasu jego trwania. Wśród tych dzieci stężenie NT-proBNP w spoczynku wyniosło średnio 17,7 ± 15,6 fmol/l, natomiast po wysiłku 20,3 ± 17,8 fmol/l ($p < 0,05$). Ciężka niedomykalność zastawki tętnicy płucnej wiązała się z wyższym stężeniem NT-proBNP w porównaniu z wartościami uzyskanymi u pozostałych chorych z grupy badanej (średnie wartości w spoczynku odpowiednio: 18,6 ± 15,0 i 4,2 ± 3,9 fmol/l, a po wysiłku: 20,0 ± 18,6 i 5,7 ± 4,6 fmol/l, $p < 0,05$).

Wnioski: Stężenie NT-proBNP u dzieci po korekcji TOF jest wyższe w porównaniu z dziećmi zdrowymi. Chorzy operowani z użyciem łaty przezpierścieniowej cechują się gorszą tolerancją wysiłku oraz wyższym stężeniem NT-proBNP w porównaniu z chorymi, u których nie zastosowano tej techniki operacyjnej. U osób z ciężką niedomykalnością zastawki tętnicy płucnej i trójdzielnej stężenie NT-proBNP jest wyższe niż u chorych bez przeciążenia objętościowego prawej komory. Ocena stężenia NT-proBNP może mieć znaczenie pomocnicze dla wyodrębnienia osób po operacji TOF zagrożonych niewydolnością serca i arytmią.

Słowa kluczowe: tetralogia Fallota, NT-proBNP, łata przezpierścieniowa

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